Remarks

Claims 1, 2, 5, 9-14, and 17 are pending in the application. Claims 1, 2, 5, 9-14, and 17 stand rejected. Claims 1 and 13 have been amended by the present response. New dependent claims 26-37 have been added. No new matter is added to the application by the present Amendment. Support for the added dependent claims can be found on page 9, lines 11-17 and page 12, line 20-page 13, line 4 of the specification. Applicant respectfully requests reexamination and reconsideration of the case. Each of the rejections levied in the Office Action is addressed individually below.

I. Rejection of claims 1, 2, 5, 11-14, and 17 as obvious under 35 U.S.C. § 103(a).

Claims 1, 2, 5, 11-14, and 17 are rejected under 35 U.S.C. § 103(a) as obvious over Bedell-Hogan et al., 1993, The Journal of Biological Chemistry, Vol. 268, No. 14, pages 10345-10350 in view of Weiss, U.S. Patent 6,277,622 and Rothstein et al., U.S. Patent 6,489,446. Examiner claims that non-recombinant tropoelastin isolated from native sources does not crosslink as efficiently as recombinant tropoelastin as produced by Bedell-Hogan et al. and thus employing recombinant tropoelastin as disclosed by Bedell-Hogan et al. to the method of treating wounds as disclosed in Weiss would have been obvious to one skilled in the art. The Examiner also claims that Rothstein et al. teach human tropoelastin variant polypeptides that may be used for crosslinking. Applicant traverses Examiner's rejection and respectfully requests its withdrawal for the following reasons:

Applicant asserts that the Examiner is incorrect in claiming that Bedell-Hogan et al. demonstrate that the crosslinkability of recombinant tropoelastin is greater than the crosslinkability of tropoelastin isolated from native sources. In support of his claim, the Examiner relies on Figure 1 of Bedell-Hogan et al. In Figure 1, Bedell-Hogan et al. compare the lysyl oxidase-mediated release of tritium from either recombinant tritiated tropoelastin or from a tritiated insoluble elastin substrate isolated from 16-day-old chick embryo aortae (Materials and Methods, page 10345). Insoluble elastin is formed when soluble tropoelastin monomers are crosslinked to each other by the catalytic action of lysyl oxidase. The fact that purified lysyl oxidase catalyzes release of tritium from non-crosslinked tropoelastin monomers more effectively than from a highly crosslinked elastin substrate is not surprising given the greater

number of unmodified lysine residues present in the tropoelastin monomers. Bedell-Hogan et al. do not isolate, nor do they attempt to isolate tropoelastin monomers from native sources, and they do not compare the relative crosslinkability of recombinant and native tropoelastin monomers, as asserted by the Examiner.

The Examiner also states that Weiss teaches that "an expression product of the invention", (i.e. lysyl oxidase), "may be included in a matrix including [a]... tropoelastin... which is... applied to the wound". The Examiner further claims that Weiss teaches that the enzyme and its substrate are simultaneously applied to a wound and that the enzyme is separate from its substrate prior to addition to the wound. The Examiner also points out that addition of lysyl oxidase would be "superfluous if the tropoelastin were already crosslinked." This remark highlights both the defect in the Examiner's argument and the reasons that Weiss, whether considered alone or in combination with Bedell-Hogan et al., cannot render obvious the present claims.

First, Applicant points out that the Examiner has selectively abstracted a quote from Weiss. The complete sentence reads: "Alternatively, an expression product of the invention may be included in a matrix including an elastin, tropoelastin and/or collagen based or amine containing matrix which is itself applied to the wound" (emphasis added). Given that Weiss considers elastin to be interchangeable with tropoelastin for his purposes, it is clear that he does not contemplate controlling crosslinking, i.e. maintaining lysyl oxidase and tropoelastin separate from one another prior to application to the wound site, as recited in the present claims. The Examiner's comment that lysyl oxidase would be superfluous if the tropoelastin were previously crosslinked does not make sense given that Weiss explicitly teaches the desirability of using lysyl oxidase together with elastin, which is already crosslinked. Weiss did not appreciate that it was desirable to control crosslinking by minimizing tropoelastin crosslinking prior to application to the wound site. The Examiner is reading this idea into Weiss through consideration of the present specification. Such hindsight is impermissible.

Applicant specifically submits that Weiss also does not teach or suggest that the lysyl oxidase and tropoelastin be kept separate prior to application to the wound. Weiss teaches that a matrix that includes lysyl oxidase and elastin or tropoelastin may be applied to the wound in order to accelerate wound healing (column 13, lines 44-57). If a matrix containing both lysyl oxidase and tropoelastin were constructed such as specified by Weiss, the tropoelastin would

immediately be subject to crosslinking by the lysyl oxidase present. Weiss does not even go so far as to suggest that the matrix be constructed immediately prior to application to the wound in order to provide the maximal amount of non-crosslinked tropoelastin. In fact, as previously noted by the Applicant, Weiss explicitly teaches including elastin in the matrix, which by definition is already crosslinked. In contrast, the present claims recite a method whereby the lysyl oxidase and the tropoelastin are kept separate until application to the wound or until immediately prior to application to the wound in order to keep the tropoelastin in a non-crosslinked state so that it will be available for crosslinking at the wound site. As previously noted by the Applicant, Weiss has not appreciated the advantage of using non-crosslinked tropoelastin to promote healing at the wound site, nor does he teach or suggest that the tropoelastin in the matrix remain available for crosslinking at the site of the wound. Indeed, by teaching that a previously crosslinked elastin should be applied to the wound, Weiss teaches directly away from this. Therefore, one of ordinary skill in the art could not rely on or be motivated by Weiss to simultaneously provide non-crosslinked tropoelastin and lysyl oxidase to the wound site in order to promote healing. Thus, Applicant asserts that the utilization of non-crosslinked tropoelastin recited in the present claims has not been taught, suggested, or even contemplated by Weiss, and as such, would not be obvious to one of ordinary skill in the art.

Examiner asserts that claims 11-14 and 17 are anticipated by Weiss by teaching various delivery systems of lysyl oxidase. Applicant submits that the rejection is obviated by the above arguments since Weiss has not taught, suggested, or even appreciated the advantages of applying lysyl oxidase together with non-crosslinked tropoelastin to the wound site such that the tropoelastin is available for crosslinking in order to promote better healing.

Furthermore, Examiner asserts that Weiss discloses a variety of mammalian and avian lysyl oxidases, and that the preferred lysyl oxidase for application to a person is the human enzyme, anticipating claim 2. Claim 2 recites a method for promoting the healing of a skin wound in which the applied tropoelastin is matched to the species of the recipient. Weiss discloses a method for high-level expression of lysyl oxidases, "preferably... a human lysyl oxidase" (column 6, lines 58-59), in foreign host cells by altering codons to eliminate codon sequences that are infrequently used in the foreign host cell. Weiss discloses no method of expressing a human tropoelastin substrate, or a tropoelastin of any other species. Additionally, in his discussion of practical applications made feasible by high-level expression of lysyl

oxidase, Weiss does not indicate that any lysyl oxidase substrates (including elastin, tropoelastin, and collagen) that may be applied to the wound should match the species of the recipient. In the absence of a teaching or suggestion by Weiss that the tropoelastin substrate should match the species of the recipient in order to promote wound healing, claim 2 is not rendered obvious.

Additionally, the Examiner states that the teachings of Weiss anticipate claim 5, which claims a tropoelastin that is comprised of "a heterogeneous mixture of tropoelastin isoforms." Weiss teaches contacting lysyl oxidase to "tropoelastin or a fragment thereof" as one embodiment of a method for crosslinking molecules that contain primary amines (column 13, lines 34-36). However, he fails to teach or suggest the utilization of a heterogeneous mixture of tropoelastin isoforms in order to promote wound healing. The use of a heterogeneous mixture of tropoelastin isoforms tailored to match the individual being treated, the particular type of wound, or the particular type of tissue has the advantage of minimizing any potential immune reaction resulting from the treatment (see page 19, line 20-page 20, line 14), as well as potentially resulting in a more natural healing process. Weiss has failed to appreciate these advantages, or any other advantage of using a heterogeneous mixture of tropoelastin isoforms, and thus cannot render obvious claim 5.

The Examiner also asserts that Rothstein et al. address the scope of the claim term "substantially identical to wild-type tropoelastin" since they teach that human variant tropoelastin polypeptides available for crosslinking by lysyl oxidase may be used in treating wounds. Applicant submits that the present amendment to claim 1 removing the term "substantially identical to wild-type tropoelastin" obviates the Examiner's rejection. Furthermore, even if the variant tropoelastin polypeptides of Rothstein et al. were combined with the other references, there is still no teaching or suggestion of applying virgin tropoelastin monomers (variant or wild-type) and lysyl oxidase to a wound such that crosslinking of the tropoelastin begins at the time of application, as recited in the present claims. Therefore, Applicant requests that the rejection be withdrawn.

II. Rejection of claim 9 as obvious under 35 U.S.C. § 103(a).

Claim 9 stands rejected under 35 U.S.C. § 103(a) as obvious over Bedell-Hogan et al., Weiss, and Rothstein et al. as applied to claims 1, 2, 5, 11-14, and 17 above, in further view of

Kagan. Examiner claims that it would have been obvious to one of ordinary skill in the art at the time of invention to repeatedly apply lysyl oxidase and its copper ion cofactor to the wound since such an artisan would have readily recognized that the enzyme might suffer loss of activity due to low physiological levels of copper ions. This is identical to Examiner's previous rejection of claim 9 with the exception that the Examiner has included the recombinant, non-crosslinked tropoelastin taught by Bedell-Hogan et al. as a part of the rejection. Since the rejection is levied exclusively against the loss of activity of lysyl oxidase as a result of low physiological copper levels, Applicant asserts that the inclusion of tropoelastin taught by Bedell-Hogan et al. in the present rejection is immaterial.

Regarding the copper-dependent activity of lysyl oxidase, Applicant asserts that claim 9 is not rendered obvious by the cited references because none of the primary references teach the simultaneous application of lysyl oxidase and tropoelastin wherein the tropoelastin has not been previously crosslinked and is therefore available for crosslinking at the site of the wound in order to promote healing. Kagan, by teaching that a copper-deficient diet can reduce native lysyl oxidase activity, does not make up for this deficiency. Thus, the combined references do not render obvious the repeated administration of lysyl oxidase and previously non-crosslinked tropoelastin.

Furthermore, it is well known to one of ordinary skill in the art that lysyl oxidase requires a tightly bound copper ion as a cofactor (see e.g., Kagan in Regulation of Matrix Accumulation, pp. 338-341). Lysyl oxidase purified from native sources would already have the copper ion bound and it would be readily apparent to one of ordinary skill in the art to provide copper during expression of recombinant lysyl oxidase from non-native sources. Metal cofactors are generally tightly bound to the enzyme and once bound, do not dissociate from the enzyme even in environments with low metal ion concentration. The lysyl oxidase applied to the wound would thus already have a copper ion bound to it, and would not lose its copper ion upon application to a wound site with a low copper concentration. Hence, Examiner's claim that it would have been obvious to repeatedly apply lysyl oxidase to the wound site in light of possible low levels of physiological copper is misguided and Applicant requests that the rejection be withdrawn.

III. Rejection of claim 10 as obvious under 35 U.S.C. § 103(a).

Claim 10 stands rejected under 35 U.S.C. § 103(a) as obvious over Bedell-Hogan et al., Weiss, and Rothstein et al. as applied to claims 1, 2, 5, 11-14, and 17 above, in further view of Khadem et al. Examiner claims that it would have been obvious to one of ordinary skill in the art at the time of invention to use sutures, staples, adhesive strips, or tissue glue, the latter taught by Khadem et al., to approximate separated wound tissues with mechanical means while simultaneously applying lysyl oxidase and non-crosslinked tropoelastin.

Applicant submits that claim 10 is not rendered obvious by the cited references because none of the primary references teach or even suggest the simultaneous application of lysyl oxidase and tropoelastin wherein the tropoelastin has not been previously crosslinked and is therefore available for crosslinking at the site of the wound in order to promote healing, as discussed above. In teaching the use of photoactivating radiation to form a tissue glue to close wounds in soft tissue, Khadem et al. do not make up for this deficiency. Additionally, there is no teaching or suggestion to combine the photoactivation method of Khadem et al. with the other references. In the absence of a teaching or suggestion to combine, a rejection based on obviousness cannot stand. Thus, Applicant requests that the rejection be withdrawn.

In view of the present arguments, Applicant respectfully submits that the present case is in condition for allowance. A Notice to that effect is thus requested.

Please charge any fees associated with this filing, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

Brenda Herschbach Jarrell, Ph.D.
Registration No. 39,223

Patent Department
Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109

(617) 248-5000
(617) 248-4000 (FAX)
Date: September 12, 2003